

# Developmental Neurotoxicology of Endocrine Disruptors and Pesticides: Identification of Information Gaps and Research Needs

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There is increasing evidence that some environmental chemicals can interrupt neurodevelopmental processes during critical periods of development, resulting in effects on sensory, motor, and cognitive function. It is now generally accepted that developing organisms are differentially sensitive to chemical exposure because of toxicokinetic and/or toxicodynamic factors. Regulatory mechanisms have been implemented to protect humans from over- or inappropriate exposures to environmental chemicals. Current regulatory practices, however, may be insufficient because of the possibility that some environmental chemicals interfere with endocrine function at key periods of neurodevelopment. In addition, a recent National Research Council (NRC) report on pesticide contamination in the diets of infants and children concluded that current regulatory practices may not sufficiently protect infants and children from the risk of pesticide exposure. The NRC report indicates that regulatory agencies might underestimate the actual exposure of infants and children to pesticides and rely too heavily on data from adults in the risk assessment of pesticides. Consideration of endocrine-disrupting chemicals and the differential susceptibility of infants and children has led to identification of a number of information gaps and research needs that should be addressed in order to improve future risk assessments for these chemicals. — *Environ Health Perspect* 106(Suppl 3):807–811 (1998). <http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-3/807-811tilson/abstract.html>

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## Neurodevelopmental Effects of Chemicals

It has been estimated that 70% of developmental defects have no known cause and that some of these defects may be related to chemical exposure acting alone or in combination with genetic or nutritional factors (1). It is now generally accepted that developmental exposure to chemicals can have adverse effects on the structure or function of the nervous system. Possible functional defects in neurodevelopment include severe and mild mental retardation, cerebral palsy, psychoses, epilepsy, abnormal neurologic development or disrupted maturational

milestones, cognitive deficits, and/or sensory dysfunction (2).

Relative to the adult, the developing nervous system is differentially vulnerable to chemical exposure (3). Selective vulnerability of the developing organism could be due to a number of factors, including differences in metabolizing enzymes, rates of excretion, lack of a protective blood–brain barrier, and differential binding affinity to target proteins. Rodier and colleagues (4,5) were among the first to argue that one reason for the differential vulnerability of the developing nervous system is that it undergoes defined periods of maturation, each

of which could be affected by chemical exposure. Neurogenesis, migration, synaptogenesis, gliogenesis, and myelination are developmental processes that have generally reached a steady state in the adult and are not potential targets for neurotoxic agents. There are several examples in the literature demonstrating that exposure to a chemical during a critical period of development will produce neurotoxicity, whereas exposure to the same chemical during adulthood will have little or no effect (4–6).

The possibility that exposure to some environmental agents could adversely affect the development of the nervous system has led to guidelines for testing chemicals for potential developmental neurotoxicity prior to marketing (7). Testing guidelines for developmental neurotoxic effects have been described by the World Health Organization (8) and developmental neurotoxicity guidelines are now under consideration by the Organisation for Economic Co-operation and Development. The U.S. Environmental Protection Agency (U.S. EPA) recently revised its developmental neurotoxicity testing guidelines to provide better guidance for experimental design and dosing, as well as information concerning the types of measurements that should be taken (9). However, the adequacy of the approaches taken to protect the public from the risk of chemical-induced developmental toxicity has been questioned by two recent developments, i.e., the hypothesis that environmental chemicals interact with endocrine systems producing a spectrum of effects in humans and animals (10), and the report by the National Research Council (NRC) (11) concluding that current regulatory procedures to assess the toxicity of pesticides may significantly underestimate the risk to infants and children.

## Neurodevelopmental Effects of Endocrine Disruptors

There is increasing evidence that chemicals in the environment affect the endocrine system (10,12). There are correlative data suggesting that specific populations of animals have been adversely affected by exposure to such environmental chemicals. Endocrine disruptors have been broadly defined as exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes (13,14).

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Abbreviations used: FQPA, Food Quality Protection Act; NRC, National Research Council; U.S. EPA, U.S. Environmental Protection Agency.

Neuroendocrine dysfunction may occur because of a disturbance in the regulation and modulation of neuroendocrine feedback systems. One major indicator of neuroendocrine function is secretion of hormones from the pituitary gland. Hypothalamic control of anterior pituitary secretions is also involved in a number of important bodily functions. Many types of behaviors (e.g., reproductive behaviors, sexually dimorphic behaviors in animals) are dependent on the integrity of the hypothalamic-pituitary system, which could represent a potential site of neurotoxicity. Pituitary secretions arise from a number of different cell types in this gland and neurotoxicants could affect these cells directly or indirectly. Morphologic changes in cells mediating neuroendocrine secretions could be associated with adverse effects on the pituitary or hypothalamus and could ultimately affect behavior and the functions of the nervous system. Biochemical changes in the hypothalamus may also be used as indicators of potential adverse effects on neuroendocrine function. Finally, the development of the nervous system is intimately associated with the presence of circulating hormones such as thyroid hormone (15). The nature of the nervous system deficit, which could include cognitive dysfunction, altered neurologic development, or sensory deficits, depends on the severity of the thyroid disturbance and the specific developmental period when exposure to the chemical occurred.

In 1991 the U.S. EPA published revised testing guidelines for *a*) a neurotoxicity screening battery, *b*) delayed neurotoxicity of organophosphorous substances following acute and 28-day exposures, *c*) schedule-controlled operant behavior, *d*) peripheral nerve function, and *e*) developmental neurotoxicity (9). Although none of these testing guidelines specifically address chemical-induced neuroendocrine dysfunction, the developmental neurotoxicity testing guidelines include measures of maternal toxicity and fetal viability as well as developmental milestones, motor activity, acoustic startle reactivity, learning and memory, and routine pathology of the offspring. Routine measures of sexual maturity are also included. This battery of developmental tests should be capable of detecting chemical-induced neuroendocrine dysfunction, particularly if used in conjunction with reproductive and developmental testing guidelines that more directly assess possible chemical-induced endocrine dysfunction. Although neuroendocrine dysfunction was not specifically mentioned in the proposed

guidelines for neurotoxicity risk assessment (16), public comment on this point led to the inclusion of a new section on neuroendocrine effects in the final version of the risk-assessment guidelines (17).

In response to growing public health concerns about chemicals in the environment that could adversely affect endocrine function, a workshop was held in 1995 to identify research needs related to the health effects that might be related to endocrine disruptors, including carcinogenicity, developmental toxicity, and neurotoxicity (13). Research needs with regard to the effects of endocrine disruptors on neurodevelopmental processes were also addressed at a subsequent conference, "Developmental Neurotoxicity of Endocrine Disruptors," held in Hot Springs, Arkansas, in 1995. At that conference Tilson and Kavlock (14) summarized the known biologic effects of endocrine disruptors, the uncertainties faced by the risk assessor in evaluating these chemicals, and the need to develop a systematic research strategy to address these uncertainties. Many of these concerns were also addressed in a workshop, "Environmental Endocrine-Disrupting Chemicals: Neural, Endocrine, and Behavioral Effects," held in Erice, Sicily, in November 1995.

As mentioned previously, it is generally accepted that disruption of endocrine function could have a number of neurodevelopmental effects, including altered reproductive behaviors mediated by the hypothalamic-pituitary axis, hypothalamically mediated body metabolism, sexual differentiation in brain morphology, and cognitive and psychomotor development. Sexual and brain development are under the influence of estrogenic and androgenic hormones and chemicals that interfere with these hormones during development can adversely affect neurodevelopment. Thyroid hormones also play an important role in the development of the nervous system, and chemical-induced alterations of thyroid function during development can produce developmental neurotoxicity (15). Moderate to severe alterations in thyroid hormone concentrations during development result in motor dysfunction, cognitive deficits, and other neurologic abnormalities. In addition, recent research (18) suggests that developmental hypothyroidism in rats can cause permanent ototoxicity.

There are several chemicals or classes of chemicals that could cause neurodevelopmental alterations by interfering with neuroendocrine function, including polychlorinated biphenyls, dioxin, and

chlorinated pesticides, some metals (e.g., methylmercury, lead, organotins), insect growth regulators, dithiocarbamates, synthetic steroids, tamoxifen, phytoestrogens, and triazine herbicides (13,14). Research is needed to determine if other chemicals or classes of chemicals affect neurodevelopmental processes by disrupting endocrine function during development. Any compounds that mimic or antagonize the actions of neurotransmitters, hormones, and growth factors in the developing brain have the potential to adversely affect neurodevelopment.

There are a number of uncertainties that must be resolved before it is possible to understand clearly the risk associated with exposure to endocrine-disrupting chemicals (13,14). For example, it is particularly problematic that exposure to most chemicals in the environment involves mixtures, making it difficult to link health effects to a specific chemical exposure. In addition, many chemicals are metabolized or undergo environmental degradation, which further complicates the association between any specific effect on neurodevelopment and a particular chemical form or species. Generally, there is little known about the distribution and metabolism of environmentally relevant chemicals or the behavior of chemicals in environmentally relevant mixtures. Systematic research is needed to address the principle of additivity in determining the risk associated with exposure to mixtures and determine the conditions under which synergistic interactions might be present. Research is also needed to determine the toxicokinetics of environmentally relevant chemicals with an emphasis on providing better exposure assessments to correlate biologic effects with target or tissue concentrations.

Another concern is that there is a wide range of possible neurodevelopmental effects that could be produced by disrupting endocrine function during development (13,14). Only a small number of possible end points have been used in studies on endocrine disruptors and it is possible that significant alterations in neurodevelopmental processes have yet to be identified. Another concern is the uncertainty about extrapolating biologic findings obtained in animals to humans. The development of the endocrine system in different species of animals and humans may be associated with the development of qualitatively different neurodevelopmental functions. It may, therefore, be problematic to determine the relevance of a chemical-induced

change in an animal to human health. In addition, there may be populations or individuals within populations that are differentially sensitive to endocrine disruptors. This issue could be addressed by coordinated epidemiologic research to exploit human and wildlife populations having well-documented exposures in order to define the most relevant biological effects to study. Identification of differential sensitivities in populations, or individuals within populations, to neuroendocrine disruptors may also be possible.

There are also a number of experimental variables that could affect identification of chemical-induced neurodevelopmental effects. For example, the time at which effects are measured following exposure could be critical (13,14). Chemical-induced neurodevelopmental effects could depend on variables such as changes in environmental temperature, hormonal status, and life-cycle stage. Neurotoxicity following developmental exposure to chemicals can vary qualitatively and quantitatively depending on the phase of nervous system maturation (4,5). Thus, a chemical could affect neurodevelopmental processes if exposure occurred during a critical period of neuroendocrine maturation, but have little or no effect if exposure occurred at some other period of development. Another experimental variable concerns the shape of the dose-response curve. It is possible that nonlinear dose-response curves could be generated for some measures of neurodevelopment and that chemicals could have multiple effects at different points on the curve. It may be problematic, therefore, to predict effects of long-term, low-level exposures from studies using short-term, high-dose exposures. Integrated field and laboratory studies focusing on critical experimental variables, such as dose-response function, critical periods of exposure, and the use of more sensitive or appropriate end points, are needed.

Finally, there is a general lack of understanding concerning the mechanisms by which endocrine disruptors could alter neurodevelopment. The effects of some endocrine disruptors could be the result of a direct action on structures mediating neuroendocrine function, whereas others may be related to effects on other organ systems that indirectly affect endocrine function. Research at the cellular and molecular level is needed to provide a better understanding of the mechanism of action for known neuroendocrine disruptors. In addition, although there is considerable

information on the maturation processes involved in normal neurodevelopment, little is known about how chemicals could disrupt these processes by interfering with neuroendocrine development. Research is needed to better understand the role that neuroendocrine systems play in the normal development of the nervous system.

Concern about the possible environmental and human health effects of endocrine disruptors has led to the formation of the Committee on the Environment and Natural Resources Working Group on Endocrine Disruptors. This group has representatives from 14 federal agencies and is charged with developing a planning framework for research, conducting an inventory of ongoing research and identifying research gaps, and developing a coordinated response plan for high priority needs. The area of endocrine disruption is also currently being assessed by the Hormone Toxicant Committee under the auspices of the National Academy of Sciences and through workshops on endocrine disruptors held in Britain, Germany, and Denmark.

In summary, the developing nervous system is differentially sensitive to many neurotoxic chemicals and exposure to environmentally relevant chemicals could adversely affect neurodevelopmental processes. The development of the nervous system is clearly dependent on appropriate endocrine-mediated signals at critical periods of maturation. Research is needed to determine the extent to which alterations in endocrine function during development may be responsible for adverse health effects observed in humans and wildlife populations.

### **Pesticides in the Diets of Infants and Children**

Pesticides are used effectively throughout the world to improve agriculture yields and protect human health. Because of the concern that over- or inappropriate exposure to these chemicals could cause adverse health effects, the Federal Insecticide, Fungicide and Rodenticide Act and the Federal Food, Drug and Cosmetic Act (9) have been enacted in the United States to regulate exposure to these agents and ensure the safety of the food supply.

Historically, studies of pesticide toxicity have been performed primarily in adult animals. However, it is now generally accepted that infants and children form a subpopulation differing from adults in their responsiveness to chemicals, suggesting that they should be considered separately in

regulatory decisions. This concern led the U.S. Congress to request that the National Academy of Sciences determine if additional consideration of the potential differences in responses by infants and children to pesticides is warranted. A committee formed by the NRC was given the responsibility of evaluating scientific and policy issues faced by governmental agencies in regulating pesticide residues in foods consumed by infants and children. One of the main conclusions in the NRC report entitled *Pesticides in the Diets of Infants and Children* (11) was that current federal regulatory practices may not adequately address age-related differences in sensitivity to pesticide-induced health effects.

The NRC report (11) also contained a number of conclusions and recommendations related to research. One conclusion was that regulatory agencies may underestimate the amount of pesticides actually consumed by infants and children. It was therefore recommended that risk assessors consider all sources of dietary and non-dietary pesticide exposure, including air, soil, lawns, pets, indoor surfaces, drinking water, and water added to foods. It was further recommended that estimates of total dietary exposure should be refined to consider exposures to multiple pesticides having common mechanisms of action. The NRC report identified the need for better data concerning the actual intake of pesticide residues by infants and children and recommended food consumption surveys be conducted for children at several age levels.

The NRC report (11) also indicated that much of the concern about age-related susceptibility to pesticides was predicated on the assumption that there were both qualitative and quantitative differences in the responses of children and adults to pesticide exposure. It was concluded, however, that data supporting this assumption were generally lacking and recommended comparative studies to evaluate the possible differences in sensitivity and toxicodynamic and kinetic variables between developing and adult animals. A clear understanding of the extent to which such differences may actually exist is needed before changes in current regulatory practices are made.

Another conclusion in the NRC report was that the toxicity testing strategies currently used by regulatory agencies are inadequate for assessing toxicity to a number of organ systems, including neurodevelopmental processes. It was recommended that because neurotoxicity is such an important consideration for the developing organism,

regulatory agencies such as the U.S. EPA should revise their published guidelines on testing for neurodevelopmental effects as new information is obtained. As mentioned previously, the U.S. EPA's developmental neurotoxicity testing guidelines (9) include several measures of maternal and fetotoxicity as well as assessments of developmental milestones, neuropathology, and sensorimotor and cognitive functioning of the offspring. Because these testing guidelines involve considerable resources and rely heavily on functional end points, they have been used infrequently. There is a need to develop more cost-effective and mechanistically based measures of developmental neurotoxicity for the routine assessment of pesticides and other compounds.

The NRC report also pointed out that the rodent is the primary species used in studies on the developmental toxicity of pesticides, and recommended studies to determine the adequacy of rodents as a test species. Careful attention to species differences in toxicodynamic variables as well as stages of maturation of the nervous system is important in assessing the adequacy of current testing strategies.

The NRC report (11) also concluded that current developmental neurotoxicity testing guidelines do not contain assessments of some potentially important neurobiologic end points such as sensory changes or alterations in sensory organs. A recommendation was made to develop a general guideline for visual system toxicity testing that can be modified and applied on a case-by-case basis. Finally, the NRC report pointed out that current testing requirements in chronic studies do not include assessment of the thyroid gland. As discussed in the section on endocrine disruptors, the thyroid is a potential target site for chemicals that alter neurodevelopmental processes. Research is needed to determine the most appropriate morphologic and biochemical measurements to be used in developmental neurotoxicity testing.

The publication of the NRC report (11) has had a significant impact on regulatory agencies in the United States. The U.S. EPA, for example, has placed an increased emphasis on children's health effects from toxic chemicals in the environment. The U.S. EPA is concerned that infants and children are still developing and are differentially vulnerable to environmental threats, and it recognizes that exposure to toxic substances could affect the development of the nervous system, causing abnormalities in neurodevelopment. It is also of

concern that children may have a greater intake of pesticides via diet and nondiet sources relative to adults and that children's behavior may result in higher levels of exposure to a variety of environmental hazards. There are also a number of known environmental health threats to infants and children, including exposure to chemicals known to affect neurodevelopment, such as lead, pesticides, methylmercury, and polychlorinated biphenyls.

The NRC report (11) has also played a significant role in helping to formulate new legislation to regulate pesticides. Many of the provisions contained in the Food Quality Protection Act (FQPA) (19) originated from recommendations made in the NRC report. For example, in setting tolerances for pesticide residues in food, the FQPA directs the U.S. EPA to consider the use of an extra 10-fold uncertainty factor to account for several factors, including the susceptibility of children; the special susceptibility of children to exposure, particularly during gestation; the cumulative effects of pesticides having similar mechanisms of action; the aggregate exposure from all routes; and the potential for endocrine-disrupting effects. There are a number of research and data needs associated with the FQPA that are based on recommendations made in the NRC report, including improving the scientific basis for using an extra uncertainty factor of 10 for infants and children; identification and characterization of age-related differences in sensitivity to chemicals; developing a strategy to assess effects related to cumulative exposure, aggregate exposure, or exposure to chemicals having similar mechanisms of action; and screening approaches for chemicals having endocrine effects.

### Developmental Neurotoxicology Workshop

The vulnerability of the developing organism to environmental factors has also become a major concern of the public health community and the environmentally active general public. To address these concerns, the National Institute for Environmental Health Sciences sponsored a Developmental Neurotoxicology Workshop on 7–9 September 1996. The overall objective of this workshop was to identify current progress in developmental neuroscience and outline potential areas and methodologies for application to developmental neurotoxicology. The participants of this workshop made several recommendations that support

the need for basic research in the area of developmental neurotoxicology, including the need: *a)* to identify and validate specific developmental proteins for use as biomarkers of developmental neurotoxicity, *b)* for multidisciplinary research at all levels of nervous system organization to correlate with behavioral deficits and mechanisms, *c)* to address the role of compensation and redundancy in the response of the developing nervous system to perturbation, *d)* to develop the use of *in vitro* approaches to identify developmental neurotoxins, and *e)* to study interactions of xenobiotics with the metabolic processing of growth factors, receptor activation, and subsequent signal transduction processes. The overall conclusion of this workshop was that information derived from basic developmental neurobiology research is critical to improve our capacity to identify chemicals that will be developmental neurotoxins.

### Summary and Conclusions

The possibility that exposure to chemicals could adversely affect the development of the nervous system and other target organs has led to a regulatory process designed to protect human health. This process, however, has been questioned by recent reports that some environmental chemicals may affect endocrine systems, producing a number of possible adverse effects in humans and animals (13). Furthermore, the NRC report (11) has raised a number of concerns about the adequacy of current regulatory practices to protect the health of susceptible populations.

Endocrine systems are essential for the normal development of the nervous system. Chemical-induced alterations in hormones involved in sexual development or growth could alter neurodevelopment, resulting in abnormal behavior, motor and sensory dysfunction, and cognitive disabilities. Research is needed to identify and characterize chemicals that act as endocrine disruptors and determine the conditions under which they alter normal neurodevelopment.

It is also recognized that the nervous system develops in specific phases or stages, making it differentially vulnerable to chemical exposure. Developing organisms may also differ in sensitivity to chemicals because of a number of toxicokinetic factors. The NRC report (11) concludes that current regulatory practices may not protect this population sufficiently. Research is needed to determine the conditions under which infants and children are differentially sensitive to chemical exposure and to

identify the chemicals that will produce developmental neurotoxicity.

Concern about protecting children from toxicants in the environment has led to the development of an enhanced focus on children's issues by regulatory agencies such as

the U.S. EPA. This agenda includes several recommendations to better protect children's health and to expand research on the unique susceptibility and differential exposure of children to environmental chemicals. In addition, significant changes

have been made in legislation concerning the regulation of pesticides. Implementation of the FQPA (19) will also lead to increased research to improve the scientific basis underlying the risk assessment of pesticides.

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